

REMARKS:

Claims 1-8 are in the case and presented for consideration.

The withdrawn claims have been canceled subject to Applicants right to file a divisional application on these claims.

Claims 1-8 have been amended to further distinguish the present invention over the prior art.

INFORMATION DISCLOSURE STATEMENT

In accordance with Examiner's comments, the prior art references cited to in the background section of the specification have been listed in an information disclosure statement, PTO/SB/08B form, which is submitted with this amendment.

We are currently waiting for our client to provide us with electronic copies of the listed references which we will file upon receipt.

ABSTRACT

The abstract has been amended in accordance with Examiner's suggestion and is therefore believed to be in proper form.

CLAIM OBJECTIONS

Claims 1, 3-5 and 7 have been amended in accordance with Examiner's comments and therefore are now believed to be in proper form.

REJECTION OF CLAIMS UNDER 35 U.S.C. §112

Claims 6-8 were rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 5-8 were amended in accordance with Examiner's suggestion and therefore are now believed to be in accord with 35 U.S.C. 112, second paragraph.

REJECTION OF CLAIMS UNDER 35 U.S.C. §§ 102(b)/103(a)

Claims 1 and 3 were rejected under 35 U.S.C. 102(b) as being anticipated by Greenwald et al. (International Publication No. WO 99/30727; Published Jun. 24, 1999) ("Greenwald") or, in the alternative, under 35 U.S.C. 103(a) as obvious over Greenwald as evidenced by Ulbrich et al. (K. Ulbrich et al., J. Controlled Release (2000) 64, p. 63-79) ("Ulbrich").

Applicants respectfully traverse the Office's rejections that the claims of the present application are either anticipated or rendered obvious by the cited prior art.

A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. See, e.g., *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). Additionally, to constitute anticipation, all the claimed elements must be found in exactly the same situation and united in the same way to perform the identical

function in a single unit of prior art. *General Elect. Co. v. Nintendo Co., Ltd.*, 179 F.3d 1350 (Fed. Cir. 1999). Moreover, it is a settled point of law that dependent claims include all the elements of the claims from which they depend.

Greenwald fails to disclose at least two critical elements claimed in currently amended independent claim 1.

The Greenwald reference is directed to the structure and synthesis of polymeric prodrugs releasing the drugs with 1,4 or 1,6 benzyl elimination reaction. Syntheses of these polymer prodrugs are described in examples 1-58 and shown in figures 1-5. However, polymeric prodrugs which release the drug via a 1,4 or 1,6 benzyl elimination reaction are not the subject matter of the present invention.

The general "hydroxypropylmethacrylamide (HPMA) and copolymers thereof" cited on page 17 of Greenwald have structures which are connected with a very specific type of activation (elimination), i.e. poly(HPMA) and have structures which are completely different from those which are claimed in the present application.

Additionally, the relevant polymer in Greenwald, mentioned in its claim 1, is described very generally as a "substantially non-antigenic polymer." Additionally, only polyalkylene oxides are mentioned in the relevant portion of the description.

The present invention deals with HPMA homopolymer with reactive and functional thiazolidine-2-thione (TT) groups randomly distributed along the polymer chain, which must be introduced into polymer structure by specific reactions. However, these necessary specific reactions are not disclosed in Greenwald.

It is commonly accepted that detailed structure and length of polymer chain

significantly control properties of each polymer molecule, especially if used as a drug carrier. Furthermore, it is also commonly known that the detailed structure and length of a polymer chain significantly controls the properties of polymer molecules, especially if it is used as a drug carrier. It is further known that both physical and chemical behavior of N-2-hydroxypropyl or N-3-hydroxypropyl group-containing monomers and related polymers vary widely depending on their particular structure.

Therefore, the general disclosure and listing of a series of polymers without more specific treatment and explanation does not read on the well-defined structures of N-(2-hydroxypropyl)-methacrylamide copolymers claimed in currently amended independent claim 1 and claim 3. Also, without more, such a disclosure would be insufficient to lead one of ordinary skill to the subject matter of the present invention.

Additionally, in the present invention the thiazolidine-2-thione groups are located along the HPMA copolymer chain. In the case of HPMA copolymers with thiazolidine-2-thione groups at the end of polymer chain, a polymerization process using an initiator with a functional group or chain transfer agent is used, enabling the conversion of this functional group to a thiazolidine-2-thione group. The residue of initiator or chain transfer agent with functional group is introduced to the end of polymer chain during the polymerization process and can not be considered a linker as that term is used in the present invention.

Moreover, it is unclear which reaction Examiner was referring to when he wrote: "The termini of these polymers may be activated with thiazolidine-2-thione groups as taught by Greenwald (examples 1, 5, 8, and 10; figures 2, 3, and 5), reading on the reactive

polymers/copolymers of instant claim 1."

Because there is no functional group at the end of HPMA polymers Examiner's statement clearly evidences a basic misunderstanding as to differences between the structure of poly(ethylene glycol)s and N-(2-hydroxypropyl)methacrylamide copolymers.

Also, Examiner's statement on page 8 and 9 that "the HPMA as taught by Greenwald is a homopolymer in at least one embodiment, in which case approximately 100% (i.e. minimally 60%) of the monomer units are hydroxypropylmethacrylamide units" is inconsistent with the correct definition of homopolymer. According to "Polymer Chemistry, Vollmert, 1973, page 22" the correct definition of homopolymer is as follows: "If only one monomer is involved in the synthesis of a macromolecule, it is called a homopolymer."

In addition, Examiner's further statement on page 9 of the above referenced action that "Greenwald teach[s] the use of thiazolidine-2-thione groups bound through the nitrogen of the thiazolidine-2-thione group to a carbonyl group that is a component of a linker at the end of the polymer chain" actually supports a finding that the present invention is novel

On page 17 Greenwald states that "polyvinyl alcohols, carbohydrate-based polymers, hydroxypropylmethacrylamide (HPMA), and copolymers thereof, etc. and the like can be used if the same type of activation is employed as described herein for PAD's such as PEG." However, this is not the case of polymers at issue in the present application.

Additionally, Examiner's statement on page 8 that "Greenwald et al. teach the use of a variety of polymers as the basis of their invention including, inter alia, hydroxypropylmethacrylamide (HPMA) and copolymers thereof (page 17, lines 6-10)," is not correct. In the entire Greenwald reference "hydroxypropylmethacrylamide and

copolymers thereof" is mentioned only once and without any further description.

Finally, Ulbrich deals with HPMA copolymers with substantially different properties than the TT group-containing copolymers of the present application. Ulbrich discloses the use of HPMA copolymers containing p-nitrophenyl esters reactive groups (ONp). In fact, it was the relative inferiority of the chemical and physicochemical behavior of the ONp polymers which motivated Applicants to conduct further research which eventually lead to the development of the TT group-bearing HPMA copolymers of the present application.

Therefore, because Greenwald fails to disclose at least two critical elements claimed in currently amended independent claim 1 and because all other claims depend either directly or indirectly therefrom, Greenwald does not anticipate any of the claims currently in the case.

Furthermore, because Ulbrich fails to supply the elements of currently amended independent claim 1 which are missing from Greenwald, and because neither Greenwald nor Ulbrich contains a teaching or suggestion which would be sufficient to lead one of ordinary skill in the art to the presently claimed invention, the combination of Greenwald and Ulbrich does not render any of the present claims obvious.

REJECTION OF CLAIMS UNDER 35 U.S.C. §103(a)

Claims 1-8 were rejected under 35 U.S.C. 103(a) as being unpatentable over Ulbrich in view of Greenwald et al. R. B. Greenwald, Bioconjugate Chern. (1996) 7, p. 638-641 ("Greenwald 1996").

Applicants respectfully traverse the Office's rejections that the claims of the subject application are obvious in view of the cited prior art.

The elements of currently amended independent claim 1 which are missing from Greenwald and Ulrich are also absent from Greenwald 1996.

Regarding Paragraphs 7, 8, and 10 on the page 12 -14, Examiner relied on data in Ulbrich which has no relation to the present invention. Moreover the calculation procedure described by Examiner is wrong because the division of molecular weight with molar ratio of monomers in copolymer is incorrect.

Regarding Paragraph 10 on the page 14, Examiner stated "Regarding claim 7, Ulbrich et al. teach the preparation of the polymer conjugates via radical precipitation copolymerization using 2,2' azobisisobutyronitrile (AIBN), a well-known radical initiator, to begin the process of polymerization (page 64, right column; page 66, right column). Ulbrich et al. teaches that the polymers of their study may have approximately 83 monomer units as discussed above" is unfortunately wrong for the following reasons.

The polymers defined in claim 7 were synthesized by radical solution polymerization initiated with 4,4'-azobis(4-cyanopentanoic acid) not with 2,2' azobisisobutyronitrile (AIBN). Moreover the basic difference between Ulbrich and the present invention is the type of radical polymerization.

The HPMA copolymers containing reactive p-nitrophenyl esters in Ulbrich were prepared with radical precipitation polymerization in acetone. By contrast, in the present

invention the HPMA copolymers with TT reactive groups were prepared with radical solution polymerization in DMSO. The radical precipitation polymerization enables preparation of HPMA copolymers containing reactive p-nitrophenyl esters with a molecular weight below 30 000 only. By contrast, the present invention enables preparation of HPMA copolymers with TT reactive groups by solution radical polymerization with molecular weight up to 200 000 as described in Reactive and Functional Polymers 66, 1525-1538 (2006).

Furthermore, Examiner's statement that "the substitution of thiazolidine-2-thione for the activating agents in the polymer conjugate system taught by Ulbrich is obvious by the reasoning applied above. Since Ulbrich et al. teach the use of AIBN to initiate the radical polymerization, it would have been prima facie obvious to one of ordinary skill in the art at the time of the invention to use AIBN as the radical initiator in conjugation with thiazolidine-2-thione per the teaching of Greenwald (1996) to initiate the polymerization reaction. The combination of these reagents would result in a (4-cyanopentanoyl)-thiazolidine-2-thione group at the chain end, reading on instant claim 7" is also incorrect. The combination of AIBN and thiazolidine-2-thione can not result in a polymer containing (4-cyanopentanoyl)-thiazolidine-2-thione group at the chain end.

Therefore, because Ulbrich and Greenwald 1996 both fail to supply the elements claimed in currently amended independent claim 1 which are missing from Greenwald, and because neither Greenwald 1996 nor Ulbrich contains a teaching or suggestion which would be sufficient to lead one of ordinary skill in the art to the presently claimed invention, the combination of Greenwald 1996 and Ulbrich does not render obvious any of the claims currently in the case.

Accordingly, the application and claims are believed to be in condition for allowance, and favorable action is respectfully requested.

No new matter has been added.

If any issues remain, the Examiner is respectfully invited to contact the undersigned at the number below, to advance the application to allowance.

Respectfully submitted,
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